ACS OMEGA

Article

Cite This: ACS Omega 2018, 3, 13290−13297

http://pubs.acs.org/journal/acsodf

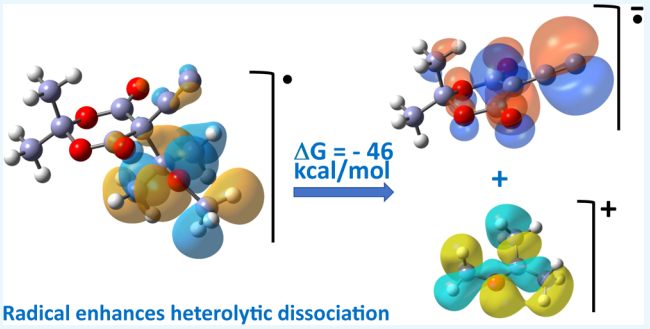
Reflex Carbocation Release from Covalent Molecules by Endogenous Free Radicals

John C. Walton*

EaStCHEM School of Chemistry, University of St. Andrews, St. Andrews, Fife KY16 9ST, United Kingdom

Supporting Information

ABSTRACT: Carbocations are pervasive in contemporary organic synthesis, so new and innocuous methods of making them are always desirable. A theoretical approach revealed that compounds in which radical generation takes place may release carbocations advantageously. The radical types and molecular substructures that promote this effect were identified. The best substructures were found to be 1,3-dicarbonyl compounds, particularly those based on the Meldrum's acid theme. Sulfate esters and dithiane rings could also be employed. Radicals generated on oxygen atoms or ethyne units were particularly effective. For these species, carbocation release could be reflex, that is, concurrent with radical generation. Only small radical enhancements were observed for release of lithium cations because of the ionic character of most of the precursors. Ethyne units could be incorporated as spacers between the radical center and the site of carbocation generation. Moreover, the enhancement was transmitted down polyethyne chains of at least six units.



Radical enhances heterolytic dissociation

INTRODUCTION

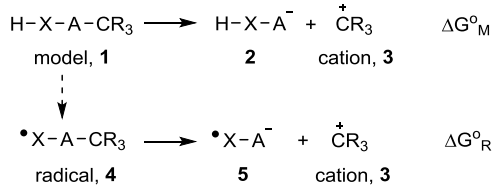
In a 1974 review, Hayon and Simic drew attention to the greater propensity of certain free radicals to deprotonate compared with parent compounds.[1] Theoretical studies have since confirmed the reality of this enhanced acidity phenomenon.[2,3] The importance of the effect as a key step in processes such as base-promoted homolytic aromatic substitution reactions[4−6] and certain one-electron redox transformations of Coenzyme A esters[7−9] has also been pointed out.

Recently, my group demonstrated that suitably sited radical centers enhanced the acidity not only of carboxylic acids but also of sulfinic and sulfonic acids. The acidity of other proton donor molecules, particularly 1,3-dicarbonyl compounds, could also be formidably increased by similar means.[10] The label "RED-shift" (for radical enhanced dissociation) was coined as a short and handy acronym to refer to the phenomenon. Radicals centered on C-, N-, and O-atoms induced RED-shifts, provided they were sufficiently close to the acid group and appropriately oriented. Huge enhancements were induced by alkoxyl radical centers and by ethynyl radical units such that 1,3-dicarbonyl compounds connected to them became carbon-based superacids.[11] Microhydration studies had revealed that acids with negative pK_as, that is, pK_as in the range of mineral acids, spontaneously dissociated on association with only a few (four or five) water molecules.[12] The authenticity of the computed RED-shifts of bicarbonate,[13] carboxyl, carboxyethynyl, and hydroperoxyl radicals was substantiated by computations of their microhydration behavior.[14]

The large magnitudes of many of the deprotonation enhancements suggested the intriguing possibility that radical centers might also induce dissociation of neutral species with release of a carbocation instead of a proton.

The process is generalized in Scheme 1 where the model compound **1** consists of a potential radical center X attached to

Scheme 1. Radical-Stimulated Carbocation Generation



a substructure A, capable of supporting a negative (−ve) charge, connected with a potential carbocation $^{+}CR_3$. The corresponding radical **4** is then an intermediate for which heterolytic dissociation to the carbocation and radical anion could be significantly enhanced. A sufficiently large enhancement might lead to spontaneous release of the cation at the moment of radical generation. Carbocation generation for Friedel−Crafts and other preparative processes usually requires the use of strong and corrosive Lewis or Brønsted acids. A likely advantage of this radical-stimulated approach would be

Received: September 7, 2018
Accepted: October 2, 2018
Published: October 16, 2018

DOI: 10.1021/acsomega.8b02307
ACS Omega 2018, 3, 13290−13297

that carbocations could be generated by the "soft" initiation methods usually applied for radicals, that is, heat, photoredox catalysis, or UV−vis irradiation.

Computational methods were employed to examine the basic premise of Scheme 1 applied to different X−A structures and with a variety of cation types. It was found that significant enhancements were indeed predicted for release of thermodynamically stabilized cations. This paper describes a method of assessing the magnitude of the effect and an investigation of what structural features in the precursors are needed for the phenomenon to occur.

RESULTS AND DISCUSSION

Quantification of Enhancement of Cation Production from Radical Precursors. Most radical intermediates are short-lived, so experimental methods for determination of the dynamics of their heterolytic cation generation would inevitably be problematic. A theoretical approach was therefore used to map the outlines of the structural and energetic constraints on the process. A computational method that would be applicable to free radicals and would be easy to apply was sought.

A previous study of 12 radical reaction types compared results from the high-level composite ab initio G4 method,[15] with those obtained with 23 different density functional theory (DFT) functionals (plus the MP2 ab initio method).[13] The CAM-B3LYP functional[16] was found to perform best with radical species and gave lowest mean absolute deviations (MADs). A second benchmarking study was carried out, this time including second row elements, specifically sulfur.[17] Free energies were obtained for 9 diverse radical reactions with 31 different DFT functionals and compared with both G4 and the extrapolated complete basis limit of a series of CCSD(T)[18−20] calculations. Comparisons of the MADs from both high-level methods indicated that M05,[21] PBE0 (PBE1PBE),[22] and LC-ωPBE[23] were the most accurate and that CAM-B3LYP also gave very satisfactory results. The CAM-B3LYP and the PBE0 functionals were chosen for this study, and full optimizations were carried out with the 6-311+G(2d,p) basis set. Solvent effects were modeled with radii and non-electrostatic terms from Truhlar and co-workers' solvent model density (SMD) solvation model and/or with the conductor-like polarizable continuum model (CPCM) model.[24]

The ease with which neutral radical **4** ionizes to carbocation **3** will certainly depend on the stabilization of the accompanying radical anion **5**. The free energies for $^{+}CR_3$ production from a radical (**4**) (ΔG°_{R}) and from the corresponding model (**1**) (ΔG°_{M}) in which the unpaired electron (upe) had been replaced by an H-atom were computed for sets of representative molecules. The difference in these quantities, $\Delta\Delta G^{\circ}$, afforded a useful measure of the enhancement

$$\Delta\Delta G^{\circ} = \Delta G^{\circ}_{M} - \Delta G^{\circ}_{R} \quad (1)$$

Positive $\Delta\Delta G^{\circ}$ values indicate radical enhancement of cation release, whereas negative values would correspond to radical inhibition of cation release.

Search for Suitable Radical Platforms. Heterolytic generation of $^{+}CR_3$ carbocations from **1** will release the same radical anion $^{\bullet}X-A^{-}$ (**5**) as that when an acid radical $^{\bullet}X-A-H$ deprotonates. As a starting point, therefore, X−A units that had been found to provide large deprotonation RED-shifts[11] were chosen for study. Scheme 2 displays the set selected to investigate release of the *t*-butyl-cation. This included carbonate ester radical **6**, propiolate ester radical **9**, sulfonate ester radical **10**, peroxyl radical **11**, the 5-methylenyl-Meldrum's acid **12**, 5-oxyl-Meldrum's acid **13** and 5-ethynyl-Meldrum's acid **14** derivatives [5-(*tert*-butyl)-5-hydroxy-2,2-dimethyl-1,3-dioxane-4,6-dione derivatives], as well as the 2-ethynyl-1,3-dithiane derivative **15**. The computed enthalpies ΔH°_{R} and free energies ΔG°_{R} for Me_3C^{+} release are in Table 1, along with the enhancement factors $\Delta\Delta G^{\circ}$.

Scheme 2. Release of *tert*-Butyl Cation from Selected Radical Platforms

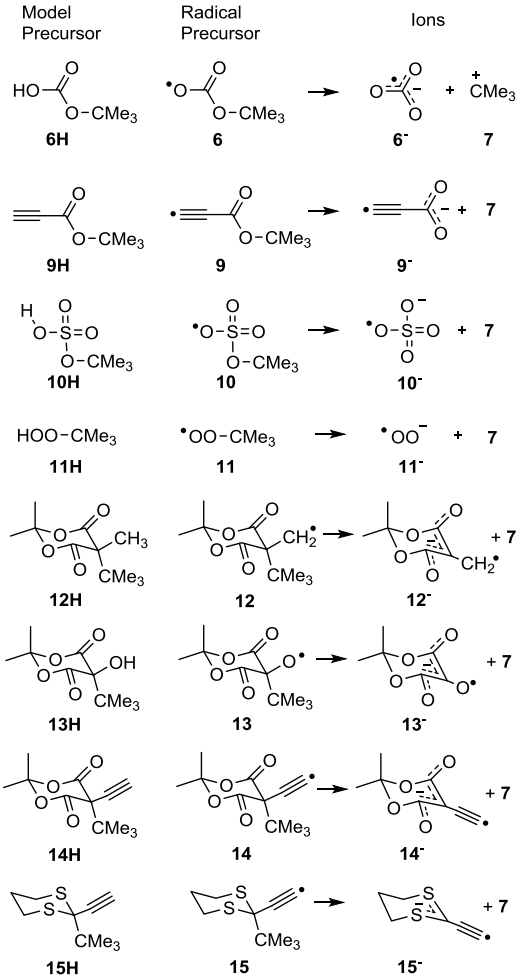


Table 1. Energetics of Release of the *t*-Butyl Cation in Water as Solvent[a]

heterolysis	DFT[b]	ΔH°_{R}	ΔG°_{R}	$\Delta\Delta G^{\circ}$
6 → **6**$^{-}$ + $^{+}CMe_3$	i	26.1	13.1	12.9
9 → **9**$^{-}$ + $^{+}CMe_3$	i	25.9	14.4	10.3
10 → **10**$^{-}$ + $^{+}CMe_3$	ii	6.3	−6.5	5.0
11 → **11**$^{-}$ + $^{+}CMe_3$	ii	43.7	31.4	12.9
12 → **12**$^{-}$ + $^{+}CMe_3$	i	17.5	5.2	12.9
13 → **13**$^{-}$ + $^{+}CMe_3$	ii	−4.0	−19.0	38.0
14 → **14**$^{-}$ + $^{+}CMe_3$	ii	−4.3	−19.1	31.3
15 → **15**$^{-}$ + $^{+}CMe_3$	i	22.1	9.14	47.8

[a]Energies in kcal/mol. [b](i) CAM-B3LYP/6-311+G(2d,p); (ii) BPE1BPE/6-311+G(2d,p).

DOI: 10.1021/acsomega.8b02307
ACS Omega 2018, 3, 13290−13297

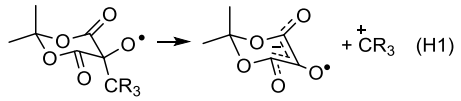
Modest enhancements (3−13 kcal/mol) were calculated for heterolytic generation of Me_3C^+ from carbonate radical **6**, propiolate radical **9**, hydrogen sulfate radical **10**, peroxyl radical **11**, and 5-methylenyl-Meldrum's acid **12**. However, four of these ionizations were endenthalpic and endergonic and so would not be practicable under mild conditions. *t*-Butyl cation release from the 2-ethynyl-1,3-dithiane radical **15** showed a very large enhancement (47.8 kcal/mol) relative to the model, but again the process was too energetically uphill for it to occur spontaneously.

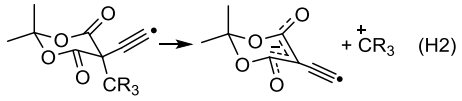
On the other hand, the releases of Me_3C^+ by the 5-oxyl-Meldrum's radical **13** and by 5-ethynyl-Meldrum's radical **14** were strongly exergonic, and large enhancements (38.0 and 33.4 kcal/mol) were predicted. The Meldrum platform appeared to be the most promising as a core structure for radical-to-cation transformations. In accord with expectation, these results also indicated that significant thermodynamic stabilization of the released carbocation would be needed for spontaneous release.

Investigation of Carbocation Suitability. In view of the favorable results obtained for Me_3C^+ release, Meldrum's linked radicals were chosen as platforms to study release of a range of cations with differing thermodynamic stabilizations. The computed energies and enhancement factors for release of some primary, allyl, benzyl, and tertiary carbocations by 5-oxyl-Meldrum's **16** (process H1) and 5-ethynyl-Meldrum's **17** (process H2) are listed in Table 2. Interestingly, the table demonstrates that the radical center enhances cation release in every case. No examples of radical inhibition of cation release were discovered.

Although allyl and benzyl cation releases (entries 4 and 6) were strongly enhanced by the radical center, both were endergonic and so experimentally impracticable. Introduction of the electron-donating MeO group led to exergonic processes for release of the primary methoxymethyl cation (both radical platforms; entries 2 and 3). Similarly, release of the 1-methoxyallyl and 4-methoxybenzyl cations (entries 5 and 8) was also exergonic. As might be expected, introduction of the MeO group to the *t*-butyl cation led to very favorable energetics (entries 9 and 10). The optimization for structure **16** (CR_3 = $Me_2(MeO)C^+$) led directly to the dissociation products radical anion $\mathbf{13}^-$ and carbocation $Me_2(MeO)C^+$. This implied that generation of radical **16** (CR_3 = $Me_2(MeO)C^+$) [and probably **17** (CR_3 = $Me_2(MeO)C^+$) as well] would lead to concerted (spontaneous) carbocation formation.

Table 2. Energetics of Release of Diverse Carbocations in Water as Solvent[a]



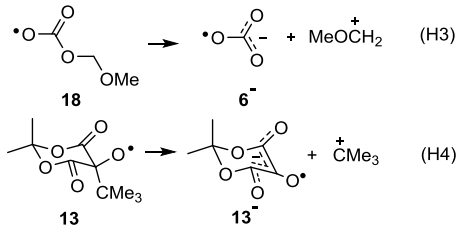


entry	process	R_3C^+	ΔH°_R	ΔG°_R	$\Delta\Delta G^\circ$
1	H2	FCH_2^+	44.0	32.3	33.5
2	H2	$MeOCH_2^+$	1.6	−10.1	33.1
3	H1	$MeOCH_2^+$	2.6	−8.7	47.3
4	H1	$CH_2{=}CHCH_2^+$	23.3	11.1	43.2
5	H1	$MeOCH5CHCH_2^+$	−5.4	−16.1	43.3
6	H1	$PhCH_2^+$	14.7	2.6	42.6
7	H1	$4\text{-}MeOC_6H_4CH_2^+$	13.0	1.3	43.2
8	H2	$4\text{-}MeOC_6H_4CH_2^+$	6.0	−5.6	33.3
9	H1[b]	$Me_2(MeO)C^+$	[b]	[b]	[b]
10	H2	$Me_2(MeO)C^+$	−27.3	−42.1	33.3

[a]Energies in kcal/mol; DFT with CAM-B3LYP/6-311+G(2d,p). [b]Dissociated straight to $\mathbf{13}^-$ and $Me_2(MeO)C^+$.

Effect of Solvent on Carbocation Release. The difference in solvation between the neutral radical precursors and the charged products was expected to have a considerable impact on the heterolytic cleavage. The magnitude of solvation effects was probed for two representative processes. First, release of the primary $MeOCH_2^+$ cation from the carbonate radical precursor **18** (process H3 in Table 3) (together with the corresponding model) was examined. Second, the release of the *t*-butyl cation from the 5-oxyl-Meldrum's radical **13** (and model) (process H4 in Table 3) was studied. The SMD method, on the basis of the quantum mechanical charge density of a solute molecule interacting with a continuum description of the solvent, was employed.[24] The free energies for the two processes, for solvents ranging from water to *n*-heptane, as well as the enhancement factors relative to the nonradical models, are recorded in Table 3.

Table 3. Effect of Solvents on Heterolytic Cation Release[a]



solvent	δ[b]	$MeOCH_2^+$ (H3)		Me_3C^+ (H4)		
		ΔG°_R	$\Delta\Delta G^\circ$	ΔG°_R	$\Delta\Delta G$	Δr(CC)[c]
H_2O	23.5	7.7	13.8	−19.0	38.0	0.112
MeOH	14.3	8.9	14.9	−15.9	37.0	0.115
DMSO	12.9	18.2	16.1	−9.6	38.5	0.096
MeCN	11.9	16.4	15.8	−11.6	40.3	0.097
$Me_2C{=}O$	9.8	20.3	15.9			
THF	9.5	31.5	16.3	0.9	38.4	0.090
$n\text{-}C_7H_{16}$	7.4	77.4	17.1	43.5	37.5	0.078

[a]Energies in kcal/mol; DFT with PBE1PBE/6-311+G(2d,p). [b]Standard Hildebrand solvent parameters in $cal^{1/2}/cm^{3/2}$. [c]Extension of the bond length in Å (radical—model) from Me_3C to the C atom of attachment in Meldrum's unit.

The free energy for $MeOCH_2^+$ release from radical **18** increased by nearly 70 kcal/mol (less favorable) as the polarity of the solvent decreased from water to *n*-heptane. No solvent was found in which this process would be exergonic. However, although the free energy of Me_3C^+ release from radical **13** increased by about 60 kcal/mol through the series of solvents, the reaction was favorably exergonic in methanol, dimethyl sulfoxide (DMSO), and acetonitrile, as well as in water. The enhancement factors $\Delta\Delta G^\circ$ for both processes H3 and H4 were positive and very substantial for H4. Interestingly, these enhancements changed by only a small amount as the solvent was varied. Not unexpectedly therefore, the change in solvation on going from the neutral model with charged products to the

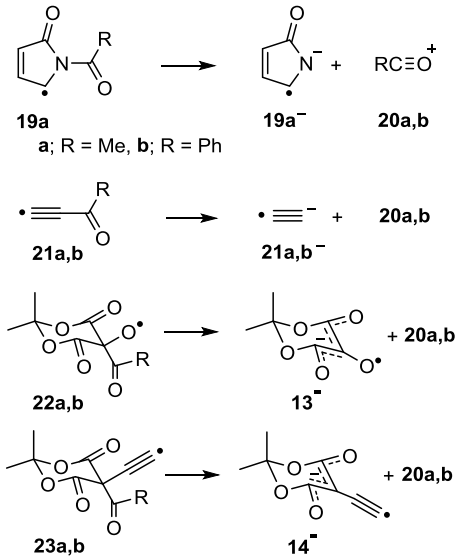
DOI: 10.1021/acsomega.8b02307
ACS Omega 2018, 3, 13290−13297

neutral radical with charged products remained fairly constant, irrespective of solvent properties. Water was unquestionably the solvent of choice for advantageous energetics. However, methanol or acetonitrile could be used, with little or no diminution in enhancement, for covalent precursors insoluble in water.

The enhancement of ionic dissociation of the 5-oxyl-Meldrum's radical (**13**) was accompanied by a lengthening of the bond from its CMe_3 group to its Meldrum's unit compared to that in the nonradical model (**13H**). Furthermore, there was a trend toward greater bond extension [Δr(CC) in Table 3] as the exergonicity increased for the more polar solvents (see Table 3). For the carbonate series (**18**) the C−O bond from the $MeOCH_2$ group to the carbonate unit was also longer in the radical than in the model but the extension, 0.011−0.015 Å, depending on solvent, was much smaller.

Release of Acylium and Lithium Cations. Radical enhancement of release of acylium and benzoylium cations was also studied for the set of precursor radicals (and corresponding models) shown in Scheme 3.

Scheme 3. Radical Platforms for Release of Acyl Type Cations



The computed enthalpies, free energies, and enhancement factors are in Table 4. The 1,5-dihydro-2*H*-pyrrol-2-one unit of **19a** was chosen because of the potential resonance stabilization of the anions produced on ionization. A modest enhancement of acylium release from radical **19a** was obtained, but the process was impractically endergonic (Table 4). Similarly, although the releases of both $PhCO^+$ and $MeCO^+$ were significantly enhanced for the ethynyl platforms **21a,b**, the energetics were again very unfavorable. However, acylium release was exergonic from both 5-oxyl-Meldrum's **22a** and 5-ethynyl-Meldrum's **23a** precursors and large enhancement factors were observed for the radicals. Release of $PhCO^+$ was also favorable for both **22b** and **23b**.

Because of the importance of lithium ions in battery technology, release of this alkali metal cation from carbonate **24**, carboxyethynyl **25**, ethynyl **26**, and Meldrum's radical-containing platforms was also examined (Scheme 4). The computed energies are in Table 5. For all of these platforms, the heterolyses were endergonic. The smallness of the enhancement factors obtained for Li^+ release from the radical forms of the carbonate and carboxyethynyl species (Table 5) can be attributed to their salt-like character. The calculated long C−Li bond (2.18 Å) in model-lithiated Meldrum's acid **27H**, together with the large positive charge on Li (0.88), indicated it was virtually an ionic compound. The C−Li bond was slightly shorter (2.07 Å) in the radical **27** and the charge on Li was smaller (0.65), suggesting lower ionic character. In conformity with this, the computed $\Delta\Delta G^\circ$ was actually

Table 4. Energetics for Release of Acylium-Type Cations in Acetonitrile[a]

heterolysis	R	ΔH°_R	ΔG°_R	$\Delta\Delta G^\circ$
19a → **19a**$^-$ + RCO^+	Me	65.2	52.8	13.2
21a → **21a**$^-$ + RCO^+	Me	54.5	45.1	19.0
21b → **21b**$^-$ + RCO^+	Ph	57.1	47.3	19.0
22a → **13**$^-$ + RCO^+	Me	0.9	−10.7	37.3
22b → **13**$^-$ + RCO^+	Ph	6.2	−4.5	26.4
23a → **14**$^-$ + RCO^+	Me	−9.6	−21.7	35.4
23b → **14**$^-$ + RCO^+	Ph	−8.3	−20.8	35.6

[a]Energies in kcal/mol; PBE1PBE/6-311+G(2d,p); scrf = SMD-(acetonitrile).

Scheme 4. Radical Platforms for Release of Lithium Cations

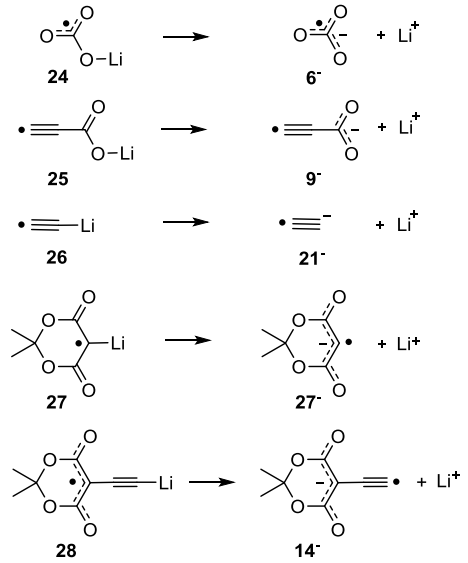


Table 5. Energetics for Release of Lithium Cations in Water and THF[a]

heterolysis	solvent	ΔH°_R	ΔG°_R	$\Delta\Delta G^\circ$
24 → **6**$^-$ + Li^+	H_2O	17.0	9.5	8.5
24 → **6**$^-$ + Li^+	THF	35.5	28.2	14.0
25 → **9**$^-$ + Li^+	THF	30.7	24.0	14.7
26 → **21**$^-$ + Li^+	H_2O	17.8	10.1	9.6
26 → **21**$^-$ + Li^+	THF	32.7	25.0	10.4
27 → **27**$^-$ + Li^+	H_2O	13.7	7.1	−3.6
28 → **14**$^-$ + Li^+	THF	37.3	30.46	3.3

[a]Energies in kcal/mol; PBE1PBE/6-311+G(2d,p).

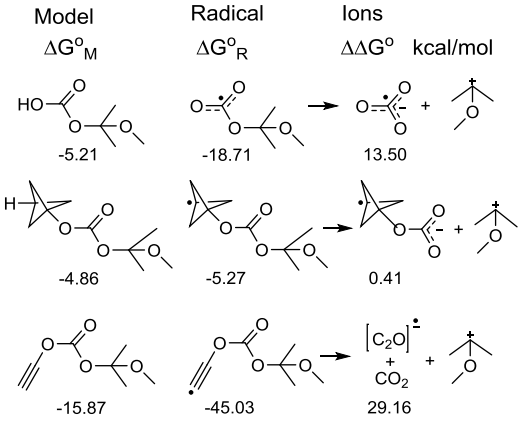
DOI: 10.1021/acsomega.8b02307
ACS Omega 2018, 3, 13290−13297

marginally negative (−3.6). For the ethynyl-Meldrum's platform, the minimum energy structure of the model had the Li-atom attached to one of the O-atoms and in the optimized radical **28**, it was attached to the terminal ethyne C atom. Not only was the process endergonic but virtually no enhancement was found (Table 5).

Influence of Ethyne Radicals and Multiple Ethyne Spacer Units. The cation release process was tolerant of the introduction of the two-carbon ethyne spacer between the upe and the cation (see tables above). The effect of lengthening this spacer by more ethyne units was therefore studied. Small hydrocarbon cages are known to transmit spin density across their centers.[25,26] The huge γ-H-atom hyperfine splitting in the electron paramagnetic resonance spectrum of the bicyclo[1.1.1]pent-1-yl radical pointed to its cage as by far the most effective.[27,28] This spacer unit was also investigated.

Scheme 5 compares the computed ΔG°_{M} and ΔG°_{R} values and the enhancement factors $\Delta\Delta G^{\circ}$, for release of the 2-methoxyprop-2-yl cation from carbonate radical, with data for the analogs with a bicyclo[1.1.1]pentane or with an ethyne spacer. Cation release from the carbonate radical was exergonic and with a modest enhancement (13.5 kcal/mol) compared with the model. With the ethyne spacer, heterolytic dissociation was computed to release the 2-methoxyprop-2-yl cation but accompanied by CO_2 and the $C_2O^{-\bullet}$ radical anion. The exergonicity was significantly increased, as was the enhancement factor. On the other hand, with the bicyclo[1.1.1]pentane spacer, $\Delta\Delta G^{\circ}$ was close to zero such that enhancement from the upe was completely suppressed.

Scheme 5. Effect of Spacers on Release of *t*-Bu Cations[a]

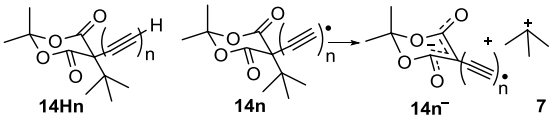


[a]Computed energies with the PBE1PBE/6-311+G(2d,p) method and the SMD solvent continuum model with water.

Because the ethyne spacer was so effective, the result of increasing the number of ethyne spacer units was also explored. Release of the *t*-butyl cation from Meldrum's precursor radicals with up to 6 ethyne spacers (**14*n***; n = 1−6) and release of the 2-methoxyprop-2-yl cation from similar precursors with up to 6 ethyne spacers (**29*n***) were examined. Additionally, release of 2-methoxyprop-2-yl cation from the 1,3-dithiane radicals **15*n*** was studied. Finally, release of lithium ions from the ethynyllithium precursors **26*n***, having up to 7 spacers, was investigated in tetrahydrofuran (THF). The computed free energies are in Tables 6−9 (see also the Supporting Information).

Release of the *t*-butyl cation from Meldrum's species **15H-1** and **15-1** was investigated using both the CAM-B3LYP and PBE1PBE methods (Table 6, top two rows). The respectable agreement of the energies obtained demonstrates the comparability of the two methods. The tables show that ΔG°_{M} for all model precursors became less endergonic (or more exergonic) as the length of the polyethynyl spacer increased. The dissociations of radicals **14*n*** to Me_3C^+ became less exergonic as the spacer increased in length, whereas the dissociation of analogous **29*n*** to $Me_2(MeO)C^+$ varied little in exergonicity (Tables 6 and 7). Loss of the $Me_2(MeO)C^+$ cation from dithiane radical **15*n*** became more exergonic as the length of the spacer increased (Table 8), but ΔG°_{M} decreased in parallel such that the enhancement decreased by only a small amount. ΔG°_{R} for loss of Li^+ from precursors **26*n*** varied little with spacer length (Table 9).

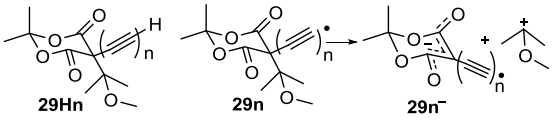
Table 6. Energetics for Release of the $^+CMe_3$ Cation (7) from Polyethynyl Meldrum's Precursors 14*n*



n	ΔG°_{M} (model **14H*n***)	ΔG°_{R} (radical **14*n***)	$\Delta\Delta G^{\circ}$	r(C−C)/Å[c]
1[a]	13.48	−19.93	33.41	
1[b]	12.26	−19.08	31.34	1.620
2[b]	9.34	−14.48	23.82	1.621
3[b]	6.63	−12.69	19.32	1.623
4[b]	6.87	−10.65	17.52	1.626
5[b]	5.12	−9.86	15.37	1.634
6[b]	4.70	−7.45	12.15	1.632

[a]CAM-B3LYP/6-311+G(2d,p) with CPCN(water). [b]PBE1PBE/6-311+G(2d,p) with SMD(water) values in kcal/mol. [c]r(C−C) is length of the bond from the platform A to the leaving cation in the radicals ($^{\bullet}$XA-cation).

Table 7. Energetics for Release of the $^+C(MeO)Me_2$ Cation from Polyethynyl Meldrum's Precursors 29*n*[a]



n	ΔG° (model **29H*n***)	ΔG° (radical **29*n***)	$\Delta\Delta G^{\circ}$	r(C−C)/Å[b]
1	−8.80	−42.05	33.25	1.613
2	−11.90	−46.08	34.18	1.614
3	−13.14	−46.30	33.17	1.614
4	−14.64	−46.40	31.76	1.614
5	−16.22	−47.56	31.34	1.614
6	−15.62	−45.64	30.02	1.614

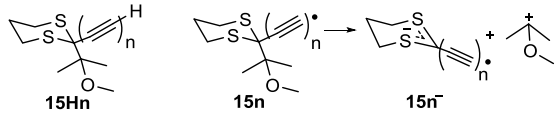
[a]CAM-B3LYP/6-311+G(2d,p) with CPCN(water); values in kcal/mol. [b]r(C−C) is length of the bond from the platform A to the leaving cation in the radicals ($^{\bullet}$XA-cation).

Large enhancement factors $\Delta\Delta G^{\circ}$ were computed for dissociation of all Meldrum's species and the dithiane precursors to carbocations. Only modest enhancements were obtained for Li^+ release from the polyethynyl precursors **26*n***. The variation in the $\Delta\Delta G^{\circ}$ enhancements as the additional spacer units were added is illustrated in Figure 1.

As expected, $\Delta\Delta G^{\circ}$ decreased for the dissociations of all radical species as the length of the polyethyne spacer chains increased. However, the remarkable result that became apparent was the ability of the spacer chains to transmit the

DOI: 10.1021/acsomega.8b02307
ACS Omega 2018, 3, 13290−13297

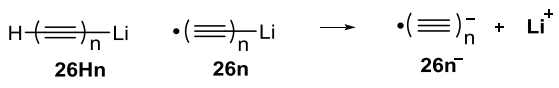
Table 8. Energetics for Release of the $^{+}C(MeO)Me_2$ Cation from Polyethynyl Dithiane Precursors 15*n* in Water[a]



n	ΔG° (model **15H*n***)	ΔG° (radical **15*n***)	ΔΔG°	*r*(C−C)/Å[b]
1	36.81	−8.22	45.03	1.562
2	29.97	−11.95	41.91	1.567
3	24.12	−16.45	40.57	1.569
4	19.83	−19.00	38.83	1.569
5	16.64	−19.91	36.56	1.569
6	16.33	−22.20	38.53	1.570

[a]PBE1PBE/6-311+G(2d,p) with SMD(water); values in kcal/mol. [b]*r*(C−C) is length of the bond from the platform A to the leaving cation in the radicals (•XA-cation).

Table 9. Energetics for Release of the Li(+) Cation from Lithium Polyethynyl Radicals 26*n* in THF[a]



n	ΔG° (model **26H*n***)	ΔG° (radical **26*n***)	ΔΔG°	*r*(C−Li)/Å[b]
1	35.32	24.95	10.37	1.993
2	32.80	26.29	6.51	2.003
3	31.05	25.23	5.82	2.005
4	30.48	25.25	5.22	2.005
5	29.20	25.13	4.07	2.005
6	29.75	25.67	4.08	2.003
7	29.79	22.65	7.14	2.002

[a]PBE1PBE/6-311+G(2d,p) with SMD(THF); energy values in kcal/mol. [b]*r*(C−Li) is length of the bond from the platform A to the leaving Li cation in the radicals (•XA−Li).

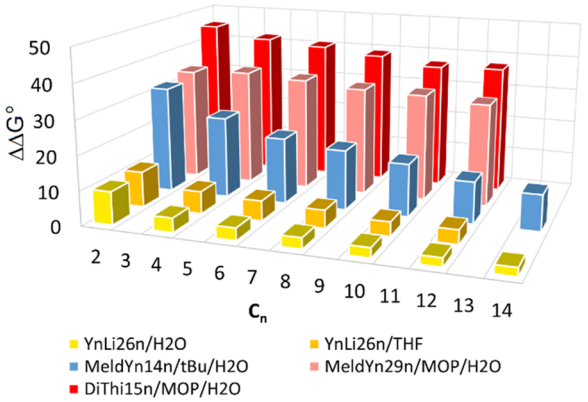


Figure 1. Plots of enhancement factors ΔΔG° (kcal/mol) as a function of the number of C atoms (C_n) in the chains of ethyne spacers for radicals **14*n***, **29*n***, **15*n***, and **26*n***.

influence of the upe through more than 6 or 7 ethyne units (up to 14 C atoms!). Dissociations to carbocations were still significantly enhanced even when the upe and breaking bond were (formally) so distant. A similar ability of polyethynyl spacers to transmit RED-shift was observed in the analogous deprotonation reactions.[11]

As mentioned above, the thermodynamic stabilities of the radical anions $^{\bullet}X-A^{-}$ (**5**) formed on release of the cations will be a key factor. These same radical anions are, of course, released in deprotonations of acid radicals $^{\bullet}X-A-H$. The distribution of charge and spin in these species will impact both their solvation and their thermodynamic stabilization. The previously observed trend was of larger RED-shifts for radicals with charge delocalized away from their anionic centers, coupled with spin density distributed toward these centers.[10,11] This same site exchange of spin with charge, in the released radical anions, undoubtedly also plays a leading role in cation release.

It might be supposed that the length of the bond from the platform A to the leaving cation in the radicals (•XA-cation), that is, *r*(C−C) for **14*n***, **29*n***, and **15*n*** and *r*(C−Li) for **26*n***, would reflect the exergonicity of cation loss. However, the computed bond lengths for the radicals of Tables 6−9 (final columns) show only very minor changes and do not correlate well with the ΔG°_{R} values.

CONCLUSIONS

The heterolytic dissociations of neutral covalent species were greatly enhanced for structures containing radical centers adjacent to potential cations. Such enhancements took place when the bonds breaking heterolytically were C−CR_3, C−C(O), O−CR_3, N−C(O), O−Li, and C−Li types. For exergonic heterolytic dissociations, *tert*-carbocations were required. Electron-releasing groups, particularly MeO substituents attached to the cationic centers, facilitated the process. Sulfate ester (**10**) and dithiane (**15**) radical platforms promoted exergonic releases of cations. However, the most successful substructures that gave exergonic heterolytic release of the widest variety of cations, were the 5-oxyl-Meldrum and 5-ethynyl-Meldrum radical types (**16**, **17** etc.). It is very probable that other 1,3-dicarbonyl core structures would work nearly as well. Spontaneous cation release, concerted with radical generation, can be anticipated for 3-methoxyallylium and 2-methoxypropylium cations from these structures. Radical enhancements of Li cation release were small for all platforms, probably because the precursors were already salt like or at least partly ionic in character. It was no surprise that cation release took place most readily in water as solvent, but methanol, DMSO, and acetonitrile also permitted large enhancements.

In every case of carbocation generation examined, the presence of an upe either enhanced the process or had little effect. No case of radical inhibition of carbocation release was found. The only retardation discovered was for Li^{+} cation generation from Meldrum-lithium radical ((2,2-dimethyl-4,6-dioxo-1,3-dioxan-5-yl)lithium, **27**), and that was very small.

For large enhancements, the radical center X and spacer A in the $^{\bullet}X-A-CR_3$ species needed to be single C, N, or O atoms. Sizeable enhancements were also achieved for X−A = O−C−O and O−S−O. The cage bicyclo[1.1.1]pentyl structure did not transmit the enhancement, and it is safe to conclude other saturated hydrocarbon spacers would also block the effect. A remarkable finding was that the ethyne spacer in almost every radical platform led to sizeable enhancements. Notably too, polyethyne spacers gave rise to long-range enhancement. Radicals generated six or seven ethyne units away from the cationic center were still effective in enhancing cation release. It is worth mentioning the complementarity of these fragmentations to those of radical substrates that see anionic leaving groups, such as acetate anions or the loss of phosphate anions from deoxyribose radicals.[29−31]

DOI: 10.1021/acsomega.8b02307
ACS Omega 2018, 3, 13290−13297

Carbocations are extremely important in contemporary organic synthesis[32] as well as in cationic polymerizations. Friedel−Crafts alkylations and acylations are amongst the most important routes to functionalized aromatic compounds. Wagner−Meerwein skeletal rearrangements, homoallylic/cyclopropyl rearrangements, pinacol rearrangements, and others remain important in syntheses of numerous natural products. Chiral carbocation couplings with nucleophiles constitute valuable routes to asymmetric syntheses. To date, for most of these processes, either strong mineral acids or corrosive Lewis acids are required. Several of the radical platforms described above have the potential to deliver a specific carbocation as a reflex on generation of the upe. No strong acids or toxic metals need to be involved, and neutral conditions will prevail. Excellent control of initiation can be achieved when the radicals are generated photochemically or by mild heating. Practical applications of the radical-induced production of carbocations can therefore be anticipated as mild alternatives for many of these preparations.

EXPERIMENTAL SECTION

DFT calculations were carried out using the Gaussian 09 suite of programs.[33] Results were obtained with two different DFT methods. First, the CAM-B3LYP functional[16] with the 6-311+G(2d,p) basis set was employed with the CPCM continuum model[24b] with water as solvent. This model is derived from the COSMO model. Default values of the keywords Alpha, Radii, TSNUM, and TSARE were employed. On the basis of previous work with free radicals, the CAM-B3LYP functional, which combines the hybrid qualities of B3LYP with the long-range correction proposed by Tawada et al.[34] gave the best results in comparison with G4 (MAD: 2.5 kcal/mol). A second benchmarking study including second row elements indicated that M05,[21] PBE0 (PBE1PBE),[22] and LC-PBE[23] were the most accurate and that CAM-B3LYP also gave very satisfactory results. Full optimizations were carried out with the PBE1PBE/6-311+G(2d,p) method. Solvent effects were modeled with radii and non-electrostatic terms from Truhlar and co-workers' SMD solvation model.[24a] Vibrational frequency calculations were implemented so that GS (no imaginary frequencies) and TS status could be checked (one imaginary frequency), and enthalpies and free energies were adjusted for zero point and thermal corrections to 1 atm and 298 K. The lowest energy structures of conformationally flexible molecules were, in most cases, estimated from related molecules computed previously.[10,11] The influence of the six-member ring conformation was shown previously to be small. In cases of doubt, the same conformation was employed for the model species as that for the radical species.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acsomega.8b02307.

Computationally obtained structures and energetics (PDF)

AUTHOR INFORMATION

Corresponding Author

*E-mail: jcw@st-andrews.ac.uk. Tel: 44(0)1334 463864.

ORCID

John C. Walton: 0000-0003-2746-6276

Notes

The author declares no competing financial interest.

ACKNOWLEDGMENTS

J.C.W. thanks EaStCHEM for financial support and Drs M. Bühl and H. Fruchtl for help with the computations. Computational support was provided through the EaStCHEM Research Computing Facility.

REFERENCES

(1) Hayon, E.; Simic, M. Acid-base properties of free radicals in solution. *Acc. Chem. Res.* **1974**, *7*, 114−121.

(2) (a) Mayer, P. M.; Glukhovtsev, M. N.; Gauld, J. W.; Radom, L. The effects of protonation on the structure, stability, and thermochemistry of carbon-centered organic radicals. *J. Am. Chem. Soc.* **1997**, *119*, 12889−12895. (b) Mayer, P. M.; Radom, L. Deprotonating molecules and free radicals to form carbon-centered anions: a G2 ab initio study of molecular and free radical acidity. *J. Phys. Chem. A* **1998**, *102*, 4918−4924.

(3) Morris, M.; Chan, B.; Radom, L. Effect of protonation state and interposed connector groups on bond dissociation enthalpies of alcohols and related systems. *J. Phys. Chem. A* **2014**, *118*, 2810−2819.

(4) Studer, A.; Curran, D. P. The electron is a catalyst. *Nat. Chem.* **2014**, *6*, 765−773.

(5) Studer, A.; Curran, D. P. Organocatalysis and C-H activation meet radical- and electron-transfer reactions. *Angew. Chem., Int. Ed.* **2011**, *50*, 5018−5022.

(6) Zhang, B.; Studer, A. Recent advances in the synthesis of nitrogen heterocycles via radical cascade reactions using isonitriles as radical acceptors. *Chem. Soc. Rev.* **2015**, *44*, 3505−3521.

(7) Buckel, W.; Keese, R. One-electron redox reactions of CoASH esters in anaerobic bacteria - a mechanistic proposal. *Angew. Chem., Int. Ed.* **1995**, *34*, 1502−1506.

(8) Smith, D. M.; Buckel, W.; Zipse, H. Deprotonation of enoxy radicals: theoretical validation of a 50-Year-Old mechanistic proposal. *Angew. Chem., Int. Ed.* **2003**, *42*, 1867−1870.

(9) Kim, J.; Darley, D. J.; Buckel, W.; Pierik, A. J. An allylic ketyl radical intermediate in clostridial amino-acid fermentation. *Nature* **2008**, *452*, 239−242.

(10) Walton, J. C. Radical-enhanced acidity: why bicarbonate, carboxyl, hydroperoxyl, and related radicals are so acidic. *J. Phys. Chem. A* **2017**, *121*, 7761−7767.

(11) Walton, J. C. Enhanced proton loss from neutral free radicals: towards carbon-centered superacids. *J. Phys. Chem. A* **2018**, *122*, 1422−1431.

(12) Leopold, K. R. Hydrated acid clusters. *Annu. Rev. Phys. Chem.* **2011**, *62*, 327−349.

(13) Bühl, M.; DaBell, P.; Manley, D. W.; McCaughan, R. P.; Walton, J. C. Bicarbonate and alkyl carbonate radicals: structural integrity and reactions with lipid components. *J. Am. Chem. Soc.* **2015**, *137*, 16153−16162.

(14) Walton, J. C. Microhydration and the enhanced acidity of free radicals. *Molecules* **2018**, *23*, 423.

(15) Curtiss, L. A.; Redfern, P. C.; Raghavachari, K. Gaussian-4 theory. *J. Chem. Phys.* **2007**, *126*, No. 084108.

(16) Yanai, T.; Tew, D. P.; Handy, N. C. A new hybrid exchange-correlation functional using the coulomb-attenuating method (CAM-B3LYP). *Chem. Phys. Lett.* **2004**, *393*, 51−57.

(17) Francis, T. The bisulfite radical - what is its lifecycle in living systems?. *MChem Dissertation*; University of St. Andrews, 2018.

(18) Čížek, J. In *Advances in Chemical Physics: Correlation effects in Atoms and Molecules*; LeFebvre, R., Mosser, C., Eds.; Wiley: Hoboken, NJ, 1969; Vol. *14*, Chapter 2, pp 35−89.

DOI: 10.1021/acsomega.8b02307
ACS Omega 2018, 3, 13290−13297

(19) Purvis, G. D.; Bartlett, R. J. A full coupled-cluster singles and doubles model: the inclusion of disconnected triples. *J. Chem. Phys.* **1982**, *76*, 1910−1918.
(20) (a) Scuseria, G. E.; Schaefer, H. F. Is coupled cluster singles and doubles (CCSD) more computationally intensive than quadratic configuration interaction (QCISD)? *J. Chem. Phys.* **1989**, *90*, 3700−3703. (b) Scuseria, G. E.; Janssen, C. L.; Schaefer, H. F. An efficient reformulation of the closed-shell coupled cluster single and double excitation (CCSD) equations. *J. Chem. Phys.* **1988**, *89*, 7382−7387.
(21) Zhao, Y.; Schultz, N. E.; Truhlar, D. G. Exchange-correlation functional with broad accuracy for metallic and nonmetallic compounds, kinetics, and noncovalent interactions. *J. Chem. Phys.* **2005**, *123*, No. 161103.
(22) (a) Adamo, C.; Barone, V. Toward reliable density functional methods without adjustable parameters: the PBE0 model. *J. Chem. Phys.* **1999**, *110*, 6158−6170. (b) Ernzerhof, M.; Scuseria, G. E. Assessment of the Perdew-Burke-Ernzerhof exchange-correlation functional. *J. Chem. Phys.* **1999**, *110*, 5029−5036.
(23) (a) Vydrov, O. A.; Scuseria, G. E.; Perdew, J. P. Tests of functionals for systems with fractional electron number. *J. Chem. Phys.* **2007**, *126*, No. 154109. (b) Vydrov, O. A.; Heyd, J.; Krukau, A. V.; Scuseria, G. E. Importance of short-range versus long-range Hartree-Fock exchange for the performance of hybrid density functionals. *J. Chem. Phys.* **2006**, *125*, No. 074106. (c) Vydrov, O. A.; Scuseria, G. E. Assessment of a long-range corrected hybrid functional. *J. Chem. Phys.* **2006**, *125*, No. 234109.
(24) (a) Marenich, A. V.; Cramer, C. J.; Truhlar, D. G. Universal solvation model based on solute electron density and a continuum model of the solvent defined by the bulk dielectric constant and atomic surface tensions. *J. Phys. Chem. B* **2009**, *113*, 6378−6396. (b) Barone, V.; Cossi, M. Quantum calculation of molecular energies and energy gradients in solution by a conductor solvent model. *J. Phys. Chem. A* **1998**, *102*, 1995−2001.
(25) Walton, J. C. Bridgehead radicals. *Chem. Soc. Rev.* **1992**, *21*, 105−112.
(26) Della, E. W.; Head, N. J.; Mallon, P.; Walton, J. C. Homolytic reactions of cubanes. generation and characterization of cubyl and cubylcarbinyl radicals. *J. Am. Chem. Soc.* **1992**, *114*, 10730−10738.
(27) Maillard, B.; Walton, J. C. An ESR study of bicyclo[1.1.1]pent-1-yl radicals. *J. Chem. Soc., Chem. Commun.* **1983**, 900−901.
(28) Adcock, W.; Binmore, G. T.; Krstic, A. R.; Walton, J. C.; Wilkie, J. Cross cage interactions in substituted bicyclo[1.1.1]pent-1-yl radicals. dissociation to [1.1.1]propellane. *J. Am. Chem. Soc.* **1995**, *117*, 2758−2766.
(29) Beckwith, A. L. J.; Phillipou, G. Stereoelectronic effects in radical fragmentation. Rearrangement of 3β,5-cyclocholestan-6-yl radical. *J. Chem. Soc. D* **1971**, 658−659.
(30) Von Sonntag, C.; Ansorge, G.; Sugimori, A.; Omori, T.; Koltzenburg, G.; Schulte-Frohlinde, D. Radiation chemistry of DNA model compounds. II. Alkyl phosphate cleavage of aliphatic phosphates induced by hydrated electrons and hydroxyl radicals. *Z. Naturforsch., B: J. Chem. Sci.* **1972**, *27B*, 471−472.
(31) Schulte-Frohlinde, D.; Bothe, E. Identification of a major pathway of strand break formation in poly U induced by hydroxyl radicals in presence of oxygen. *Z. Naturforsch., C* **1984**, *39C*, 315−319.
(32) Naredla, R. R.; Klumpp, D. A. Contemporary carbocation chemistry: applications in organic synthesis. *Chem. Rev.* **2013**, *113*, 6905−6948.
(33) Frisch, M. J.; Trucks, G. W.; Schlegel, H. B.; Scuseria, G. E.; Robb, M. A.; Cheeseman, J. R.; Scalmani, G.; Barone, V.; Petersson, G. A.; Nakatsuji, H.; Li, X.; Caricato, M.; Marenich, A.; Bloino, J.; Janesko, B. G.; Gomperts, R.; Mennucci, B.; Hratchian, H. P.; Ortiz, J. V.; Izmaylov, A. F.; Sonnenberg, J. L.; Williams-Young, D.; Ding, F.; Lipparini, F.; Egidi, F.; Goings, J.; Peng, B.; Petrone, A.; Henderson, T.; Ranasinghe, D.; Zakrzewski, V. G.; Gao, J.; Rega, N.; Zheng, G.; Liang, W.; Hada, M.; Ehara, M.; Toyota, K.; Fukuda, R.; Hasegawa, J.; Ishida, M.; Nakajima, T.; Honda, Y.; Kitao, O.; Nakai, H.; Vreven, T.; Throssell, K.; Montgomery, J. A., Jr.; Peralta, J. E.; Ogliaro, F.; Bearpark, M.; Heyd, J. J.; Brothers, E.; Kudin, K. N.; Staroverov, V. N.; Keith, T.; Kobayashi, R.; Normand, J.; Raghavachari, K.; Rendell, A.; Burant, J. C.; Iyengar, S. S.; Tomasi, J.; Cossi, M.; Millam, J. M.; Klene, M.; Adamo, C.; Cammi, R.; Ochterski, J. W.; Martin, R. L.; Morokuma, K.; Farkas, O.; Foresman, J. B.; Fox, D. J.. *Gaussian 09*, revision D.01; Gaussian, Inc.: Wallingford CT, 2016.
(34) Tawada, Y.; Tsuneda, T.; Yunagisawa, S.; Yanai, T.; Hirao, K. A long-range-corrected time-dependent density functional theory. *J. Chem. Phys.* **2004**, *120*, 8425−8433.

DOI: 10.1021/acsomega.8b02307
ACS Omega 2018, 3, 13290−13297